PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/001710	20.01.2005	21.01.2004

International Patent Classification (IPC) or both national classification and IPC
A61P31/04, A61P31/12, A61K31/506, A61K31/519, A61K31/517, A61K31/505, A61K31/496

Applicant
EMORY UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/001710

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3 (part), 6-9, 10-15 (part), 16, 17, 18-20 (part), 21, 22; 1-25 (with respect to IA)

because:

☒ the said international application, or the said claims Nos. 1-25 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-3 (part), 9-15 (part), 17-20 (part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/001710

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-3 (part), 4-8,9-15 (part), 16,17-20 (part), 21-26

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6,10,12-15,18,20,23-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III.

The whole set of clams relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Preliminary objection

It has to be noted by the applicant that number 24 in the claims is repeated twice. Since the total number of claims is 26, claims 24, 24 and 25 have to be renumbered 24, 25 and 26.

The following comments are related to the claims as originally filed.

Re Item IV.

This Authority considers that there are 7 inventions covered by the claims indicated as follows:

1. Claims 1-3 (part), 4, 5, 10-15 (part), 18-20 (part), 23, 24, 25, 26 directed to the use of pyrimidine derivatives (with a monocyclic core) for the manufacture of a medicament for treating bacterial and viral infections.
2. Claims 1-3 (part), 6-8, 10-15 (part), 16, 18-20 (part), 21, 22 directed to the use of pyrido[2,3-d]pyrimidine derivatives (with a bicyclic core) for the manufacture of a medicament for treating bacterial and viral infections,
3. Claims 1-3, 9-14, 17-19 (all partially) directed to the use of ZD6474, gefinitib or erlotinib for the manufacture of a medicament for treating bacterial and viral infections,
4. Claims 1-3, 9-14, 17-19 (all partially) directed to the use of ZK222584 for the manufacture of a medicament for treating bacterial and viral infections,
5. Claims 1-3, 9-14, 17-19 (all partially) directed to the use of CP547632 for the manufacture of a medicament for treating bacterial and viral infections,
6. Claims 1-3, 9-14, 17-19 (all partially) directed to the use of BMS354825 for the manufacture of a medicament for treating bacterial and viral infections,
7. Claims 1-3, 9-14, 17-19 (all partially) directed to the use of Su11248 for the manufacture of a medicament for treating bacterial and viral infections,

The above-mentioned groups of inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reason:
The problem underlying the present application is to provide a medicament to be used in the treatment of bacterial and viral infections.
In order to solve the problem posed, the following solutions can be found in the present application, namely:

1. the use of pyrimidine derivative with a monocyclic core according to the general formula given in claim 23,
2. the use of pyrido[2,3-d]pyrimidine derivatives with a bicyclic core,
3. the use of ZD6474, gefinitib or erlotinib (with a common quinazolone core),
4. the use of ZK222584,
5. the use of CP547632,
6. the use of BMS354825,
7. the use of SU11248.

The concept linking together the above-mentioned groups of inventions is the fact that they are tyrosine kinase inhibitors and, because of that, they can be used for the treatment of bacterial or viral infections.
However, said linking concept is already part of the state of the art since document WO03/035059 discloses the use of pyrimidine derivatives in the treatment of bacterial infections and describes their mechanism of action through the inhibition of tyrosine kinase.

Since the linking concept is known and since the compounds claimed in the present application have different structures and belong to different classes of active agents, the requirement of unity of invention is not fulfilled.

Re Item V.

Reference is made to the following documents:

D1: WO 03/035049 A (AB SCIENCE; MOUSSY, ALAIN; KINET, JEAN-PIERRE) 1 May 2003 (2003-05-01)

D2: EP-A-0 564 409 (CIBA-GEIGY AG; NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHA) 6 October 1993 (1993-10-06)

D3: TANG P ET AL: "Listeria monocytogenes, an invasive bacterium, stimulates MAP kinase upon attachment to epithelial cells" MOLECULAR BIOLOGY OF THE CELL 1994 UNITED STATES, vol. 5, no. 4, 1994, pages 455-464, XP002331177 ISSN: 1059-1524

D4: DUMENIL G ET AL: "Interferon [alpha] inhibits a Src-mediated pathway necessary for Shigella- induced cytoskeletal rearrangements in epithelial cells" JOURNAL OF CELL BIOLOGY 16 NOV 1998 UNITED STATES, vol. 143, no. 4, 16 November 1998 (1998-11-16), pages 1003-1012, XP002331178 ISSN: 0021-9525

D5: SELBACH M ET AL: "Src is the kinase of the Helicobacter pylori CagA protein in vitro and in vivo" JOURNAL OF BIOLOGICAL CHEMISTRY 01 MAR 2002 UNITED STATES, vol. 277, no. 9, 1 March 2002 (2002-03-01), pages 6775-6778, XP002331179 ISSN: 0021-9258

D6: QIE L ET AL: "Herpes Simplex Virus Entry Is Associated with Tyrosine Phosphorylation of Cellular Proteins" VIROLOGY, ACADEMIC PRESS,ORLANDO, US, vol. 256, no. 2, 10 April 1999 (1999-04-10), pages 220-227, XP004439971 ISSN: 0042-6822

D7: EP-A-1 201 765 (AXXIMA PHARMACEUTICALS AKTIENGESELLSCHAFT) 2 May 2002 (2002-05-02)

D8: HUANG M ET AL: "Inhibition of Bcr-Abl kinase activity by PD180970 blocks constitutive activation of Stat5 and growth of CML cells" ONCOGENE 12 DEC 2002 UNITED KINGDOM, vol. 21, no. 57, 12 December 2002 (2002-12-12), pages 8804-8816, XP002346291 ISSN: 0950-9232

D9: DORSEY J F ET AL: "Interleukin-3 protects Bcr-Abl-transformed hematopoietic progenitor cells from apoptosis induced by Bcr-Abl tyrosine kinase inhibitors" LEUKEMIA 2002 UNITED KINGDOM, vol. 16, no. 9, 2002, pages 1589-1595, XP002346292 ISSN: 0887-6924

D10: KRAKER A J ET AL: "Biochemical and cellular effects of c-Src kinase-selective pyrido[2,3- d]pyrimidine tyrosine kinase inhibitors"

BIOCHEMICAL PHARMACOLOGY 01 OCT 2000 UNITED STATES, vol. 60, no. 7, 1 October 2000 (2000-10-01), pages 885-898, XP002346293 ISSN: 0006-2952

D11: WO 01/45751 A (THE SCRIPPS RESEARCH INSTITUTE) 28 June 2001 (2001-06-28)

D12: US-B1-6 596 746 (DAS JAGABANDHU ET AL) 22 July 2003 (2003-07-22)

For what concerns the most relevant paragraphs of the above-mentioned documents, please see citations in the International Search Report, unless otherwise indicated.

The applicant's attention is drawn to the fact that claims, or part of the claims, relating to inventions in respect of which no International Search Report has been established won't be the subject of an International Preliminary Examination (Rule 66.1(e) PCT).

In particular, for what concerns the present application, a Partial Search Report, where only claims 1-3 (part.), 4-8, 9-15 (part.), 16, 17-20 (part.) and 21-25 have been searched, was issued. Therefore, only an opinion with respect to the searched subject-matter will be given.

The subject-matter which was excluded from the search was related to inventions 3-5 and 7 for which no supplementary search fee was paid.

Said subject-matter should be deleted from the claims (Art. 34(3)(a) and Rule 68.2 PCT).

1. NOVELTY

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6, 10, 12-15,18, 20, 23-25 is not new in the sense of Article 33(2) PCT.

1.1 First Invention

Claims 1-3 (part), 4, 5, 10-15 (part), 18-20 (part), 23, 24, 25, 26 directed to the use of pyrimidine derivatives (with a monocyclic core) for the manufacture of a medicament for treating bacterial and viral infections.

Document **D1** already discloses the use of tyrosine kinase inhibitors, in particular STI-571

(see formula on page 9) for the treatment of bacterial infections, in particular those caused by E. Coli and Salmonella typhimurium (see page 10, first par.).

1.2 Second Invention

Claims 1-3 (part), 6-8, 10-15 (part), 16, 18-20 (part), 21, 22 directed to the use of pyrido[2,3-d]pyrimidine derivatives (with a bicyclic core) for the manufacture of a medicament for treating bacterial and viral infections

Document **D7** discloses the use of pyrido[2,3-d]pyrimidine derivatives for preventing or treating Human Cytomegalovirus infections and associated diseases.

1.3 Further comments

Claim 2 does not seem to be consistent with the rest of the application since it refers to the treatment of chronic myelogenous leukemia which is a different disease than any bacterial or viral infections.

In any case, documents D8 and D9 already disclose the use of tyrosine kinase inhibitors for the treatment of CML, therefore destroying the novelty of claim 2.

2. INVENTIVE STEP

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-25 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 First Invention

Claims 1-3 (part), 4, 5, 10-15 (part), 18-20 (part), 23, 24, 25, 26 directed to the use of pyrimidine derivatives (with a monocyclic core) for the manufacture of a medicament for treating bacterial and viral infections.

The document **D1** is regarded as being the closest prior art to the subject-matter of the claims and discloses the use of tyrosine kinase inhibitors, in particular STI-571 for the treatment of bacterial infections, in particular those caused by E. Coli and Salmonella typhimurium.

The subject-matter of claims 3, 11, 13-15 and 19 differs from this known D1 in that (a) a specific family of tyrosine kinase (claims 11, 14 and 19) and (b) specific viruses (claims 10

and 13-15) are mentioned.
However, **D2** already teaches that compounds according to formula I inhibit specific tyrosine kinase, in particular the abl family (see page 5, first par.).
D3 teaches that tyrosine kinase inhibitors can be used against Listeria monocytogenes and EPEC, while D4 refers to the implication of tyrosine kinase in the invasion of cells by Shigella flexneri.
D5 discloses the mechanism of action of a Src specific tyrosine kinase inhibitor in Helicobacter pylori.
D6 (see page 224, left hand col., second par.) discloses the use of a PTK inhibitor in the reduction of HV1 and 2 expression.

The available prior art already specifies that the family of tyrosine kinase (namely abl or Src) is to be targeted in order to treat bacterial infections and teaches the use of tyrosine kinase inhibitors for the treatment of specific bacterial and viral infections; therefore, the whole set of claims relative to the first invention cannot be considered as involving any exercise of inventiveness.

2.2 Second Invention
Claims 1-3 (part), 6-8, 10-15 (part), 16, 18-20 (part), 21, 22 directed to the use of pyrido[2,3-d]pyrimidine derivatives (with a bicyclic core) for the manufacture of a medicament for treating bacterial and viral infections
Documents **D8 to D11** teach the inhibitory activity of different compounds claimed in the present application (PD serie) on Blc-Abl and c-Src tyrosine kinase.
The skilled person would therefore combine the teachings of D1 (namely the use of tyrosine kinase inhibitors for the treatment of specific bacterial and viral infections) without any exercise of inventive skills in order to get to the claimed invention.

2.3 Sixth Invention
Claims 1-3, 9-14, 17-19 (all partially) directed to the use of BMS354825 for the manufacture of a medicament for treating bacterial and viral infections
Document **D12** discloses that BMS354825 is an inhibitor of the Src-family tyrosine kinase.
The combination of the teachings of D12 and D1 leads to the claimed invention without any exercise of inventive skills.

3. INDUSTRIAL APPLICABILITY

For the assessment of the whole set of claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.